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09/727,480	12/04/2000	Sara Alajem	00/21400	4363

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GE Ehrlich 1995 LTD
Anthony Castorina
2001 Jefferson Davis Highway
Suite 207
Arlington, VA 22202

EXAMINER
FREDMAN, JEFFREY NORMAN

ART UNIT	PAPER NUMBER
1655	4

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Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No. 09/727,480	Applicant(s) Alajem et al
	Examiner Jeffrey Fredman	Art Unit 1655

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *three* MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136 (a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1) ☒ Responsive to communication(s) filed on *Dec 26, 2001* .

2a) ☐ This action is **FINAL.** 2b) ☒ This action is non-final.

3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

Disposition of Claims

4) ☒ Claim(s) *1-86* is/are pending in the application.

4a) Of the above, claim(s) *1-13, 27-40, 56-70, and 85* is/are withdrawn from consideration.

5) ☐ Claim(s) _____ is/are allowed.

6) ☒ Claim(s) *14-26, 41-55, 71-84, and 86* is/are rejected.

7) ☐ Claim(s) _____ is/are objected to.

8) ☐ Claims _____ are subject to restriction and/or election requirement.

Application Papers

9) ☐ The specification is objected to by the Examiner.

10) ☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

11) ☐ The proposed drawing correction filed on _____ is: a) ☐ approved b) ☐ disapproved.

12) ☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

13) ☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

a) ☐ All b) ☐ Some* c) ☐ None of:

1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____ .
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

*See the attached detailed Office action for a list of the certified copies not received.

14) ☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

15) ☒ Notice of References Cited (PTO-892)
16) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
17) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s). _____
18) ☐ Interview Summary (PTO-413) Paper No(s). _____
19) ☐ Notice of Informal Patent Application (PTO-152)
20) ☐ Other:

DETAILED ACTION

Election/Restriction

1. Applicant's election without traverse of Group II, claims 14-26, 41-55, 71-84, 86 in Paper No. 3 is acknowledged.

Claim Rejections - 35 USC § 112

2. Claims 14-26 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

It is vague and indefinite what is meant by the phrase "said first, second, third and fourth regions of the oligonucleotide or assembly of oligonucleotides being selected such that upon hybridization under said predetermined hybridization conditions of said first region and said second region with said target nucleic acid sequence, said first duplex structure dissociates and a second portion of said third region and a second portion of said fourth region form a second duplex structure therebetween" in claim 14. This is an extremely complicated phrase and it is unclear in a number of different ways. First, while there is antecedent basis, it is unclear what the second portions are limited to in this context. That is, it is unclear what specific structural elements differ between these two duplexes necessarily. For purposes of the prior art rejections, this claim will be interpreted such that two duplexes are formed, a first duplex which is denatured and then gives rise to a second duplex that has a restriction site.

Claim Rejections - 35 USC § 102

3. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless --
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

4. Claims 41-49, 71-78 and 86 are rejected under 35 U.S.C. 102(b) as being anticipated by Hogan et al (U.S. Patent 5,451,503).

Hogan teaches a method for detecting the presence or the absence of a target nucleic acid sequence in a sample (column 6 and column 35, claim 1) comprising the steps:

a) mixing the sample with an assembly of oligonucleotides where there is a first and second regions which are target specific and third and fourth arm regions which are linked to the first and second regions, respectively, and which hybridize to form a duplex which contains an endonuclease cleavage site (see figure 1A) or with a single oligonucleotide (see figure 4A) which are capable of forming a duplex structure by hybridization of the two arm regions which do not hybridize with the target oligonucleotide (for figure 1A) or by formation of the stem loop as per figure 4A upon hybridization to the target sequence (columns 7-9 and column 35, claim 1)

b) adding a cleaving agent, either a nuclease (column 36, claim 6) or a restriction endonuclease (column 37, claim 7) where "restriction endonuclease cleavage of a site created by duplex formation between complementary arm regions" (column 6, lines 50-52), and where the

nuclease may include RNAse H, which cleaves only the RNA strand and not the DNA strand, thus cleaving only a single strand (column 4, lines 21-54),

c) monitoring the presence or absence of cleavage products (column 36, claim 6, column 37, claim 7 or column 6, line 31 to column 7, line 24).

Hogan expressly teaches the instance where cleavage of the arm regions reduces the stability of the complex, thereby resulting in dissociation of the probe regions from the target (column 21, lines 33-42).

Hogan expressly teaches the use of modified nucleotides in the probes such as phosphorothioates which prevent cleavage by the cleaving agent (column 6, lines 11-26).

Hogan further expressly teaches that this dissociation can enable a second assembly to hybridize with the target sequence (column 21, lines 39-42).

Hogan teaches the use of two regions of the same polynucleotide. (See figure 1a, for example). Hogan also expressly teaches multiplexing this assay to detect multiple targets (column 18, lines 61-68).

Hogan teaches a probe which is self annealing (see figure 4A).

Hogan teaches the use of a variety of labels including chemiluminescent acridine ester labels (see column 6, line 66 to column 7, line 24) where the label requires the use of chemical hydrolysis of the substrate. Hogan also teaches the use of S1 nuclease detection which is an enzyme substrate based detection method (column 6, lines 45-55). Hogan further teaches the use of radioactive moieties in detection such as ^{32}P (column 22, example 13, line 44).

5. Claims 14-19, 41-44, 46, 48, 49, 71-73, 75, 77, 78 and 86 are rejected under 35 U.S.C. 102(b) as being anticipated by Lizardi et al (U.S. Patent 5,118,801).

Lizardi teaches a method for detecting the presence or the absence of a target nucleic acid sequence in a sample (column 15, claim 1) comprising the steps:

a) mixing a sample with an assembly of oligonucleotides to form a reaction mixture (see figures 8 and 11 and column 14, lines 5-26) where there is a first and second regions which are target specific (both regions within reference no. 24 in figure 8, also see column 14, lines 5-26) and third and fourth arm regions (reference no. 25 and 26 in figure 8, also see column 14, lines 5-26) which are linked to the first and second regions, respectively, and which hybridize to form a duplex (see figure 8) which are capable of forming a duplex structure by hybridization of the two arm regions which do not hybridize with the target oligonucleotide (for figure 8) where, upon hybridization of the first and second target regions to with the target nucleic acid sequence, said first duplex structure dissociates (see figure 11, where reference no. 25 and 26 are not hybridized, also see column 14, lines 5-26), and a new duplex is formed between a second oligonucleotide in the assembly and one of the dissociated duplex strands which includes an RNAse cleavage site, that is absent from the first duplex structure (figure 11). Also see figure 12, where reference No. 32 and 33 form a duplex which dissociates upon interaction with the target such that a new duplex, identified by Ref. 36 is formed which is a ribozyme cleavage site, teaching that the method of Example IV, B can be performed with a single oligonucleotide, as well as multiple oligonucleotides (and also serving to teach the limitations of claim 14),

b) adding a cleaving agent such as RNAse H (column 14, lines 5-26) which cleaves only the RNA strand and not the DNA strand, thus cleaving only a single strand.

c) monitoring the presence or absence of cleavage products (column 14, lines 5-26).

Lizardi teaches the use of detection moieties such as fluorescent molecules and radioactive molecules (column 2, lines 9-15).

Claim Rejections - 35 USC § 103

6. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(f) or (g) prior art under 35 U.S.C. 103(a).

7. Claims 41-55, 71-84 and 86 are rejected under 35 U.S.C. 103(a) as being unpatentable over Hogan et al (U.S. Patent 5,451,503) in view of Tyagi et al (U.S. Patent 5,925,517).

Hogan teaches the limitations of claims 41-49, 71-78 and 86 as discussed above. Hogan does not teach the use of a fluorescent interacting pair such as EDANS and DABCYL for detection purposes.

Tyagi teaches that EDANS and DABCYL are preferred label moieties for nucleic acid detection (column 11, lines 45-55).

It would have been *prima facie* obvious to one having ordinary skill in the art at the time the invention was made to utilize the fluorescent labels of Tyagi in the detection method of Hogan because Hogan states "More generally, it will be readily recognized that any method that detects the formation of branched DNA or the formation of a complementary arm duplex, can be utilized in this method to indicate the presence of target (column 6, lines 61-65)". Thus, an ordinary practitioner would have been motivated by Hogan to use any method which can detect duplex DNA and Tyagi teaches that "Our most preferred label moietieis are the fluorescent moiety 5-[(2-aminoethyl)amino]napthalene-1-sulfonic acid (EDANS) and quenching moiety 4-(4-dimethylaminophenylazo)benzoic acid (DABCYL). For EDANS and DABCYL, quenching is essentially eliminated by a separation of 60 angstroms, which is equivalent in length to about 20 nucleotide pairs in a double-helical nucleic acid. Thus in the preferred embodiment in figs. 1 and 2, target complemnt sequence 2, comprising 2a and 2b should be at least 20 nucleotides long (column 11, lines 44-53)". An ordinary practitioner would see that Tyagi teaches a method of determining whether a hybridization event had occurred and that this preferred label pair could be utilized as a general method to detect whether the probes interacted to form branched DNA.

8. Claims 14-26, 41-44, 46, 48-55, 71-73, 75, 77-84 and 86 are rejected under 35 U.S.C. 103(a) as being unpatentable over Lizardi et al (U.S. Patent 5,118,801) in view of Tyagi et al (U.S. Patent 5,925,517).

Lizardi teaches the limitations of claims 14-19, 41-44, 46, 48, 49, 71-73, 75, 77, 78 and 86 as discussed above. Lizardi does not teach the use of a fluorescent interacting pair such as EDANS and DABCYL for detection purposes.

Tyagi teaches that EDANS and DABCYL are preferred label moieties for nucleic acid detection (column 11, lines 45-55).

It would have been *prima facie* obvious to one having ordinary skill in the art at the time the invention was made to utilize the fluorescent labels of Tyagi in the detection method of Lizardi because Tyagi teaches that "Our most preferred label moietieis are the fluorescent moiety 5-[(2-aminoethyl)amino]napthalene-1-sulfonic acid (EDANS) and quenching moiety 4-(4-dimethylaminophenylazo)benzoic acid (DABCYL). For EDANS and DABCYL, quenching is essentially eliminated by a separation of 60 angstroms, which is equivalent in length to about 20 nucleotide pairs in a double-helical nucleic acid. Thus in the preferred embodiment in figs. 1 and 2, target complemnt sequence 2, comprising 2a and 2b should be at least 20 nucleotides long (column 11, lines 44-53)". An ordinary practitioner would see that Tyagi teaches a method of determining whether a hybridization event had occurred and that this preferred label pair could be utilized as a general method to detect whether the probes interacted to detect the target nucleic acid.

Conclusion

9. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Jeffrey Fredman, Ph.D. whose telephone number is (703) 308-6568.

The examiner is normally in the office between the hours of 6:30 a.m. and 4:00 p.m., and telephone calls either in the morning are most likely to find the examiner in the office.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, W. Gary Jones, can be reached on (703) 308-1152.

Any inquiry of a general nature or relating to the status of this application should be directed to the Group receptionist whose telephone number is (703) 308-0196.

Papers related to this application may be submitted to Technology Center 1600 by facsimile transmission via the P.T.O. Fax Center located in Crystal Mall 1. The CM1 Fax Center numbers for Technology Center 1600 are either (703) 305-3014 or (703) 308-4242. Please note that the faxing of such papers must conform with the Notice to Comply published in the Official Gazette, 1096 OG 30 (November 15, 1989).

Jeffrey Fredman
Primary Patent Examiner
Art Unit 1655

January 17, 2002